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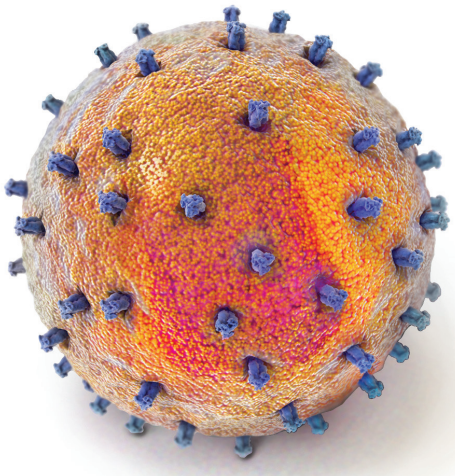

[SPOTLIGHT]

The View from the Mothership

Global HIV Vaccine Enterprise Director William Snow reflects on the past and ponders the future course for the organization, and the field of HIV vaccine research overall. ***By Mary Rushton***

Fifteen years into the AIDS pandemic, the world got a triple-dose of good news. Highly active antiretroviral therapy (HAART)—the combination of drugs to treat HIV infection—was incredibly effective and it rescued millions of HIV-infected people from the brink of death. The success with HIV treatment continues today with newer classes of drugs and drug combinations that are highly effective and less burdensome than the earliest therapies.

The search for a safe and effective vaccine is taking much longer, unfortunately. HIV is a complex virus that outruns and outmaneuvers the immune response and presents a great challenge to vaccine developers. Almost all of the vaccine candidates tested to date have failed. The only trial to show any protection against HIV was the RV144 trial in Thailand and the regimen tested in this trial was only modestly effective (31.2%).

No candidate thus far has been capable of inducing antibodies against most circulating HIV strains, the so-called broadly neutralizing antibodies that most researchers think would be necessary for an ideal vaccine. But scientists have been making remarkable progress toward developing antibody-based vaccine candidates. Recent developments in stabilizing the virus and in understanding how antibodies develop during the course of natural HIV infection is fueling vaccine science (see *VAX* July 2015 *Spotlight* article, *Inching Closer to Neutralizing Antibody-based Vaccines*). Meanwhile, scientists are continuing to build on what they learned from the RV144 trial and are developing modified candidates to test in future efficacy trials.

William Snow

Amidst all of this, the Global HIV Vaccine Enterprise, headquartered in New York City and led by long-time AIDS vaccine advocate William Snow, is trying to accelerate the pace of research, primarily through increasing dialogue and facilitating collaborations among the major players in the field. The Enterprise doesn't fund research, sponsor trials, or develop candidates. What it does is try to troubleshoot issues and provide forums for the field to reach consensus on critical issues. The Enterprise's Timely Topics in HIV Vaccine Research, launched in 2012, regularly convenes expert panels to analyze and respond to unresolved questions that encroach upon vaccine development. The series kicked off with a session on the ethics of pediatric clinical trials that led to a paper in the scientific press. Another topic was therapeutic vaccines, which figure prominently in the emerging field of HIV cure research. Lately, innovation and product development issues are at the forefront of the Enterprise's collective concerns. The Enterprise's Secretariat also meets regularly with funders and industry leaders and organizes the bi-annual HIV Research for Prevention (HIVR4P) meeting, which replaced the annual AIDS Vaccine meeting that ended in 2013. HIVR4P is the only meeting focusing solely on HIV prevention.

Like HIV vaccine researchers themselves, the Enterprise has struggled over the years. Before Snow took the helm as Director in 2012, there were questions about how

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the organization could stay focused and remain relevant (see *VAX* Nov. 2011 *Global News* article, *Global HIV Vaccine Enterprise Changes Course*). The Enterprise was conceived in 2003 by an alliance of organizations that wanted to speed up the search for an HIV vaccine through mutual coordination, collaboration, and the sharing of knowledge. This lofty premise gave way to six working groups that developed roadmaps and recommendations for the field and an interim Enterprise Secretariat, led by José Esparza, was established and housed at the Bill & Melinda Gates Foundation.

Some were critical then that the Enterprise was primarily led by the Gates Foundation. The Enterprise's Board of Directors also had a hard time finding a permanent director to lead the Secretariat. There were doubts whether the Enterprise would be able to meet the challenge of its first Scientific Strategic Plan, published in 2005, that called for a doubling of research dollars and unprecedented coordination among independent researchers to allow intellectual property and data to flow freely. Alan Bernstein, the founding president of the Canadian Institutes of Health Research and the Enterprise's first director, led the organization from 2007-2011 but was largely viewed as ineffective in executing the Enterprise's plans.

Nelson Michael, director of the US Military HIV Research Program and a member of the Enterprise's Board of Directors, said following Bernstein's departure there was a serious discussion about whether the Enterprise should even exist. "There was a very strong voice within this relatively small board that maybe we had done the experiment, that it had failed, and that it was time to move on," Michael recalls. "The view was that the Enterprise, for better or for worse, had become expensive and was not particularly well connected with its primary mission."

The Enterprise found its footing with Snow, a self-proclaimed gadfly with enormous credibility in the field. Snow's passion for ending the epidemic is matched only by his willingness to ask tough questions without apology. Though not a scientist, his roots in AIDS vaccine research run deeper than many. In what he calls a "personal journey," Snow's involvement in the famous activist group ACT-UP and with community advisory boards for clinical trials led him to co-found the HIV prevention advocacy group AVAC in 1995. He also sits on the AIDS Vaccine Research Subcommittee of the US National Institute of Allergy and Infectious Diseases (NIAID), and the US National Institutes of Health's (NIH) Vaccine Research Center Scientific Advisory Working Group. Snow also served on the Enterprise's original council and as treasurer of its board when it received its first round of funding.

Michael believes that were it not for Snow's selection, the Enterprise would have been disbanded. "He worked in partnership with the board and the funders to carve out why the Enterprise should exist," says Michael. "And for a guy without formal scientific training, he really has an intuitive understanding of the disease and the epidemic, from scientific to psychosocial. At meetings we have attended he'd often say, 'If we were to ask this question and get this answer, how would it really help us to move the ball forward to make a vaccine for HIV?' He was masterful at that."

VAX recently spoke with Snow about the early days of the Enterprise, where it is heading, and his views on the current HIV prevention landscape.

Q: *You are involved in so many groups and committees. Why did you take on the responsibility of running a non-profit like the Enterprise?*
William Snow: I saw it as a golden opportunity to try to do some of the things that I always thought ought to be, and could be, done. I had always played the role of the gadfly, so this was almost like it was meant to be. I think the partners knew they needed someone who knew the field, who got along well with people, had the history and the background, and who could promote the principles and ideals of the Enterprise. I am proud to have been representing the Enterprise for this period of time, but it really is a collaboration of organizations that don't necessarily have to collaborate with each other and it is our job to facilitate that.

Q: *Were you always a supporter of the Enterprise concept?*
WS: Yes. I thought that there was a need for more organization, high-level participation, and strategic thinking, so it sounded like an incredible opportunity from the beginning. And the individuals who signed on to that and stuck with it through the formation of the Enterprise were exactly the right people to lead that effort—top leaders in the field with the ability to influence change.

Q: *Weren't there some who wanted the Enterprise modeled after the Human Genome Project?*
WS: Yes, there was a lot of talk about that when I was on the steering committee, but it turned out that that [Human Genome Project] was really more of an engineering, heavy lifting, big numbers kind of thing. I think of the Enterprise as more ambitious, really, and less certain.

Q: *Was there much disagreement at first on the role of the Enterprise?*
WS: The initial proposal [described in 2003] proposed creating centers of excellence. But, early on, people began to realize that was unrealistic. So the idea evolved to be a more virtual network. The ultimate intention was to create a Scientific Strategic Plan for the field. That was done before the Enterprise Board started looking for a director. The strategic plan really laid the foundation for

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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996, IAVI works with partners in 25 countries to research, design and develop AIDS vaccine candidates. In addition, IAVI conducts policy analyses and serves as an advocate for the AIDS vaccine field. For more information, see www.iavi.org.

the NIH to create CHAVI [The Center for HIV/AIDS Vaccine Immunology] and for the Gates Foundation to create the CAVD [Collaboration for AIDS Vaccine Discovery].

Q: *What do you consider to be the Enterprise's biggest accomplishment?*
WS: I think there is no question that its biggest accomplishment was getting people to work together. To this day its greatest impact has been just changing the way scientists and funders work among themselves. Basically, the funders got the idea early on to create mechanisms and make funds available for investigators and institutions to work together for the common good.

Q: *What were the biggest obstacles to all this change?*
WS: There was a fair amount of resistance to the notion of giving large amounts of money to big groups of people. That was a real change from the model where people were getting their own funding and working independently at their institution or with a few close collaborators. I think for people working in HIV vaccines, and also for the funders, it was really a new way of doing things, and it took a while for that concept to prove itself. Also, during this time, NIAID opened its Vaccine Research Center. So there were big tectonic shifts on how we were working on this [HIV vaccine] problem. And like any shift, there was a lot of adjustment over what I would say was a period of six to seven years. Let me also say that there was the issue of shared samples, shared data, and confidentiality agreements. That added a whole lot of infrastructure to each consortia and required a lot of heavy lifting. A few key people dedicated themselves to the Enterprise ideal, especially Helene Gayle, José Esparza, and Siobhan Malone who gave it a healthy start within the Gates Foundation with strong support from NIAID leadership, and Peggy Johnston when she was there.

Q: *What impact did the RV144 results have on the Enterprise?*
WS: It was a major surprise for the Enterprise. They had just drafted a second Strategic Plan. The ink was drying and then RV144 happened. And the [vaccine] search turned on a dime to follow up on the results. The Enterprise's board met to figure out how to make the Enterprise more flexible and contribute to this effort rather than focus on a strategic plan. The notion was that there were more discrete areas that you could work on in real time. I think that the effect on the Enterprise was very much reactive and prompted it to change direction.

Q: *What's come out of the Timely Topics events?*
WS: Certainly, the focus we have had on industry has been important and valuable. People are realizing more and more that there are good reasons why industry isn't involved extensively in HIV vaccine research, and good reasons why some of the things they know and techniques that they use are important to the field, so the field is going to have to learn to access them another way. In the end, however, industry's knowledge is still going to be essential to making a deployable vaccine. There is no easy away around this because the only organization, outside of product development companies, that ever developed its own vaccines used to be the Army.

Q: *What about the Enterprise's other core functions?*
WS: We have what is beginning to be a healthy Funders Alliance program, where funders meet and share information and talk about common issues. Just this year, we transformed that function from an annual meeting to more of an ongoing conversation. The other big thing we do is the conferences, including HIVR4P.

Q: *What's in store for the Enterprise going forward?*
WS: In the near future, we are looking at doing more work in Africa, where we're trying to help set up a virtual network for African scientists. We're focusing a bit more on the clinical side, and we're also looking a little bit more at animal models. I believe we've proven our worth, but remember, the Enterprise is the collective of organizations and their achievements. Longer term we want to stay current, which means anticipating the needs of the field. Our focus will always be strategic rather than strictly scientific, and the prospects for a rich product pipeline have never been better. To misquote Pogo, "Them is us."

Q: *Where is the field of AIDS vaccines headed?*
WS: I think there is no question that we are on a path where we will get answers to certain questions in the predictable future that will be hugely important. That will help us to narrow down the directions we want to go in and help us to better understand what is going on with neutralizing antibodies and the RV144 model. Also, some new approaches and platforms may be transformative. The biggest handicap has always been how long it takes to do certain things—to get animal studies done, to get human endpoints and samples, etc. The field is really paying attention and trying to speed up the iterative process and I think that it is going to bear fruit.

Q: *Do oral PrEP and test and treat lessen the need for an AIDS vaccine?*
WS: I think you know the answer to this as well as I do. Every time Dr. Fauci [NIAID Director] talks he explains that none of these are long-term permanent solutions and that we need multiple pathways to prevention and cure in order to tackle this [epidemic] in an affordable and effective way. And I think there is a lot of agreement on that.

Q: *Will the rollout of oral PrEP make vaccine trials more complicated?*
WS: Yes, but this notion that it is bad for clinical trials is kind of silly. It's just a question of having to be smarter in how we design these trials.

Q: *What does the funding landscape look like for AIDS vaccines?*
WS: There is the funding landscape for vaccines and the funding landscape for HIV, and they overlap. There is a lot of interest in vaccines and more and more recognition of how valuable they are and how much they can change the world. There are new overall efforts to make new and better vaccines, especially against intractable diseases. In terms of HIV, I think there is less AIDS exceptionalism. The novelty has worn off.

Q: *But there still is a great urgency to develop one, right?*
WS: Oh my gosh, yes. I think if you took every teenager to Africa the world would be a different place. George Bush and Bono saw what it was like. Bill Gates saw what it was like. That is why we are where we are today. ■

Mary Rushton is a freelance writer based in Cambridge, Massachusetts.

[PRIMER]

Understanding Microbicide Development

What progress is being made in the development of vaginal microbicides? *By Kristen Jill Kresge*

Since the discovery of HIV nearly 35 years ago, scientists have been pursuing multiple approaches to prevent the virus from spreading. Some of these approaches are highly effective at blocking transmission and have contributed to the steady decline in the number of new HIV infections that has occurred in the past decades in many parts of the world.

In addition to adult male circumcision and risk-reduction counseling, treatment, as researchers long expected, is one of the best forms of prevention. Several studies in different populations have confirmed that if HIV-infected individuals are on suppressive antiretroviral (ARV) therapy they are as much as 96 percent less likely to transmit the virus to others. Based on these findings, the World Health Organization (WHO) now recommends that all HIV-infected individuals be offered ARV treatment at the time of their diagnosis. The organization's previous guidelines recommended treatment commence once the individual met certain threshold criteria.

The same ARV drugs that are the crux of treatment are also an effective means of prevention when administered orally to uninfected individuals. This strategy, referred to as pre-exposure prophylaxis or PrEP, has been shown to prevent HIV infection in 12 efficacy trials involving multiple populations, including serodiscordant couples (where one person is HIV infected and the other isn't), heterosexual men and women, men who have sex with men, injection drug users, and transgendered women. Based on the overwhelming effectiveness of PrEP when used consistently, last year the WHO recommended that PrEP be offered as an HIV prevention strategy to all individuals at substantial risk of HIV infection.

Researchers are also interested in microbicides that would deliver ARV drugs directly into the vagina in an effort to prevent sexual transmission of HIV. These ARV-based microbicides are being administered not as vaginal creams or gels that were once the mainstay of microbicide development, but rather via vaginal rings that eliminate the need to apply a gel or take a pill on a daily basis or around sex. This strategy may offer multiple advantages over some of the earlier microbicide candidates that proved unsuccessful in stopping HIV transmission.

ARVs are the way to go

For decades HIV prevention advocates, funders, and researchers viewed development of a vaginal microbicide as a priority. But several microbicide candidates tested in clinical trials failed to work. Two microbicide candidates—the spermicide Nonoxynol-9 and the HIV entry inhibitor cellulose sulfate—were actually shown to increase the risk of HIV transmission because of their disruptive effect on the genital cells that form a physical barrier to HIV particles. SAVVY, another microbicide gel candidate, was ineffective in blocking HIV transmission and was associated with a higher incidence of reproductive adverse events in a clinical trial.

In 2009, however, researchers were buoyed by the results from a clinical trial in South Africa that tested the efficacy of an ARV-based microbicide. This trial, known as CAPRISA 004, evaluated a topical gel formulation of the ARV tenofovir in nearly 900 women and found that it reduced HIV infection rates by 39 percent. At this time oral PrEP was still being evaluated so this trial provided the first positive results that an ARV-based prevention strategy could be effective.

Researchers then embarked on two confirmatory trials of the tenofovir gel microbicide. The FACTS 001 trial tested the same gel as CAPRISA 004 in a larger cohort of more than 2,000 South African women. Another trial, known as Vaginal and Oral Interventions to Control the Epidemic or the VOICE study, tested both oral and topical PrEP in more than 5,000 women from South Africa, Zimbabwe, and Uganda. Use of the tenofovir gel was not associated with any reduction in HIV infection rates in either of the confirmatory studies, disappointing researchers and advocates alike. The reason for the lack of efficacy was apparently that women failed to use the gels consistently. Adherence, researchers surmised, was the biggest factor in the microbicide's failure.

Researchers were simultaneously exploring other means of administering an ARV-based microbicide, including development of vaginal rings. These rings, which have been used to deliver hormonal contraception since 2001, slowly release the drug over a month's time, thereby eliminating the need to take a pill consistently around sex. The rings are made of a flexible silicone material and are inserted into the vagina by the woman. Results from at least one pivotal Phase III trial of a vaginal ring containing the experimental ARV dapivirine are expected in a few weeks when researchers and clinicians gather in the US city of Boston for the annual Conference on Retroviruses and Opportunistic Infections.

Dapivirine is an ARV that was not licensed for HIV treatment by its original developer (Janssen Sciences Ireland UC, formerly Tibotec Pharmaceuticals) because it isn't absorbed well when given orally. In 2004, Tibotec granted the rights to dapivirine to the International Partnership for Microbicides, which is the organization leading one of the Phase III trials of a vaginal ring containing the drug. This study, known as the Ring Study, involves nearly 2,000 women from South African and Uganda. The other Phase III trial, ASPIRE, is being led by the Microbicide Trials Network and involves 2,600 women from Malawi, Uganda, South Africa, and Zimbabwe.

In addition to vaginal rings researchers are also investigating vaginal films—Band-Aid sized sheets that are inserted into the vagina—containing antibodies against HIV that are capable of inactivating many of the viral strains in circulation. These so-called broadly neutralizing antibodies are the types of antibodies vaccine researchers hope to be able to induce through vaccination. There are also several long-acting, injectable ARVs in development that may be a viable means of HIV prevention.

For microbicide researchers it is very clear that more HIV prevention options are still needed. According to the Joint United Nations Programme on HIV/AIDS's 2014 Gap Report, nearly half of the 5,000 new HIV infections reported daily across the globe occur in women and girls despite the proven efficacy of oral PrEP and other HIV prevention strategies. ■

Based on an article by Mary Rushton in IAVI Report, *Vol. 19, Issue 4.*